



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Journal Pre-proof

Heterogeneidad de la severidad de hipoxemia de acuerdo a oximetría de pulso y gases arteriales en neumonía COVID-19

Isaac Núñez MD Adrian Soto-Mota MD PhD



PII: S0210-5691(21)00219-9

DOI: <https://doi.org/doi:10.1016/j.medin.2021.10.004>

Reference: MEDIN 1713

To appear in: *Medicina intensiva*

Received Date: 18 July 2021

Accepted Date: 6 October 2021

Please cite this article as: Núñez I, Soto-Mota A, Heterogeneidad de la severidad de hipoxemia de acuerdo a oximetría de pulso y gases arteriales en neumonía COVID-19, *Medicina intensiva* (2021), doi: <https://doi.org/10.1016/j.medin.2021.10.004>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.

**Article type:** Scientific letter

**Title:** Heterogeneity of hypoxemia severity according to pulse oximetry and blood gas analysis in COVID-19 pneumonia

Heterogeneidad de la severidad de hipoxemia de acuerdo a oximetría de pulso y gases arteriales en neumonía COVID-19

**Authors:**

Isaac Núñez MD<sup>1</sup>

Adrian Soto-Mota MD, PhD<sup>2</sup>

1. Departamento de Medicina Interna, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, México.
2. Unidad de Investigación de Enfermedades Metabólicas, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, México.

**Corresponding author:**

Isaac Núñez MD, Departamento de Medicina Interna, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga # 15, Belisario Domínguez Sección XVI, Tlalpan, Ciudad de México, México, Postal Code 14080. Email: isaac.nunezs@incmnsz.mx.

Pneumonia is the hallmark of severe COVID-19 [1]. Strain in healthcare systems across the world has forced countless hospitals to conduct grueling triages to decide who gets to be admitted when healthcare saturation was rampant [2]. As these decisions are inherently complex, numerous risk scores and predictor factors have been described to aid the attending medical team [3–5]. These often include clinical and laboratory values.

One commonly utilized criteria to determine patient severity is the severity of hypoxemia [6]. This can be assessed with arterial oxygen pressure (PaO<sub>2</sub>), PaO<sub>2</sub> to inspired fraction of oxygen (FiO<sub>2</sub>) ratio, arterial oxygen saturation (SatO<sub>2</sub>), pulse oximeter oxygen saturation (SpO<sub>2</sub>), SatO<sub>2</sub> to FiO<sub>2</sub> ratio, SpO<sub>2</sub> to FiO<sub>2</sub> ratio, and the prescribed oxygen device [7].

The use of these criteria for hypoxemia severity in non-intubated patients has been criticized given the expected high inter-patient variability in FiO<sub>2</sub>, shunt fraction, and physician's choice of oxygenation device and oxygen flow [7]. Therefore, relying on these criteria is suboptimal given the low comparability between different patients.

In this study, we aimed to compare the severity of hypoxemia in patients with severe COVID-19 according to oxygenation index arriving at an emergency department.

We performed a retrospective cohort study collecting information on every patient who arrived at the emergency department (ED) of a reference COVID-19 tertiary center between April 1<sup>st</sup>, 2020, and April 30<sup>th</sup>, 2021. At arrival, every patient had to go through a triage station where vital signs (including SpO<sub>2</sub>) were documented before entering the emergency department. Once in the emergency department, all patients who had low SpO<sub>2</sub> (usually < 92%) received supplemental oxygen. Only nasal cannula and non-rebreathing masks were available at our center. Arterial blood gas analysis was performed in all patients with suspected COVID-19. Generally, FiO<sub>2</sub> was estimated heuristically by the treating physician by adding to the baseline FiO<sub>2</sub> (21%) 3% for every extra liter of oxygen per minute [8]. For example, a patient receiving 2 liters of minute of supplemental oxygen would have a calculated FiO<sub>2</sub> of 27% ( $21 + 3 \times 2$ ). SpO<sub>2</sub> was obtained at ambient air, while arterial blood gas was obtained almost universally when patients received supplemental oxygen. Given the closeness between SpO<sub>2</sub> and blood gas analysis, we believe it is reasonable to assume that the clinical status of the patient is comparable between these two circumstances.

We obtained data about PaO<sub>2</sub>, SatO<sub>2</sub>, SpO<sub>2</sub>, and FiO<sub>2</sub>, with which we calculated PaO<sub>2</sub>/FiO<sub>2</sub>, SatO<sub>2</sub>/FiO<sub>2</sub>, and SpO<sub>2</sub>/FiO<sub>2</sub>. All SpO<sub>2</sub> were taken at triage with a Nihon MU-631RK portable monitor, and as such, were ambient-air (FiO<sub>2</sub> 21%). SpO<sub>2</sub>/FiO<sub>2</sub> was included to better compare oxygenation indexes. Blood gas analysis was performed in the emergency department with the RADIOMETER ABL90 flex analyzer, which directly measured SatO<sub>2</sub> and PaO<sub>2</sub>. Oxygen device used at the time of the arterial blood gas analysis could not be confidently determined, so it was not included. Since the low reliability of FiO<sub>2</sub> is the most criticized aspect of using the oxygenation device as a marker of hypoxia severity, it does not affect our analysis.

We categorized a patient's hypoxemia severity by quintiles of SpO<sub>2</sub>/FiO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, and SatO<sub>2</sub>/FiO<sub>2</sub> (from now on referred to as "oxygenation indexes"). Lower values indicate a higher hypoxemia severity. We determined strength of concordance between oxygenation index quintiles with chord diagrams across all three oxygenation index pairs. We calculated Spearman correlation coefficients for the three possible pairs of oxygenation indexes. We built scatterplots and used locally weighted scatterplot smoothing regression to graphically represent the data.

All analyses were conducted with R software version 4.0.0. The study was approved by the Research in Humans ethics committee of the author's institution.

A total of 23,049 triage visits occurred during the study period, corresponding to 19,644 individual patients. Of these, 8,123 were due to suspected COVID-19. Among 4,663 patients that were finally admitted to the ED, arterial blood gas analysis was obtained for 2,960 patients.

Median FiO<sub>2</sub> was 0.34 (inter-quartile range [IQR] 0.25-0.60), PaO<sub>2</sub> 68 mmHg (57-84), SatO<sub>2</sub> 94% (91-97), SpO<sub>2</sub> 83% (73-88), PaO<sub>2</sub>/FiO<sub>2</sub> 211 (124-281), SatO<sub>2</sub>/FiO<sub>2</sub> 274 (160-364), and SpO<sub>2</sub>/FiO<sub>2</sub> 395 (348-419). Correlation among oxygenation indexes is shown in **Figure 1**. A strong correlation was seen between PaO<sub>2</sub>/FiO<sub>2</sub> & SpO<sub>2</sub>/FiO<sub>2</sub> ( $\rho = 0.6$ ,  $p < 0.001$ ), and SatO<sub>2</sub>/FiO<sub>2</sub> & SpO<sub>2</sub>/FiO<sub>2</sub> ( $\rho = 0.65$ ,  $p < 0.001$ ), while a very strong correlation was seen between PaO<sub>2</sub>/FiO<sub>2</sub> & SatO<sub>2</sub>/FiO<sub>2</sub> ( $\rho = 0.88$ ,  $p < 0.001$ ). None of the variable pairs showed a linear relationship. All oxygenation indexes showed a considerable cross-over among quintiles (**Figure 2**), with only 785 (26.5%) patients being in the same severity quintile across all indexes.

Our study shows there is considerable heterogeneity when classifying hypoxemia severity with different oxygenation indexes. While good correlation was observed among the three evaluated pairs, the lower correlation between SpO<sub>2</sub>/FiO<sub>2</sub> and the others could be due to inaccuracy of pulse oximeters when used in patients with low oxygen saturation, physician imprecision when estimating FiO<sub>2</sub>, and/or mixed blood in the gas analysis [9]. It is likely multiple factors are involved in most cases, which is consistent with the previously mentioned concerns [7]. For example, if solely based on SpO<sub>2</sub> at triage, a patient could be wrongly classified as having a more severe disease, giving preference to a patient in better condition. Also, follow up could be hard if it is done only with oxygenation parameters. The morning medical team could classify the patient with a given severity with blood gas analysis, while the evening group could use a pulse oximeter and determine intubation is indicated.

Degree of hypoxemia is not a good measure when considered by itself in non-intubated patients with COVID-19 pneumonia, as considerable variation occurs depending on whether pulse oximetry or blood gas analysis is utilized.

#### **Data availability**

Code used for the analysis will be freely available in the un-blinded version. Data will be made available upon reasonable request to the corresponding author.

**Acknowledgements**

The authors would like to thank the triage personnel of their institution for their invaluable work during the pandemic, as well as an anonymous reviewer for helpful comments to improve the manuscript.

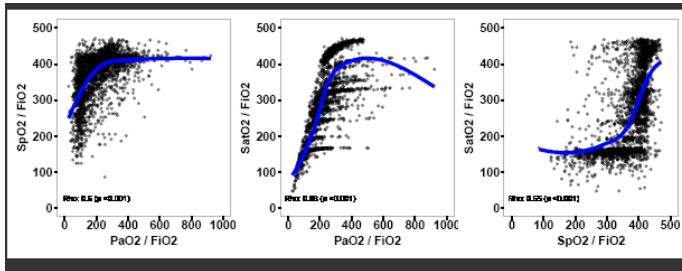
**Conflicts of interest and sources of funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest.

## REFERENCES

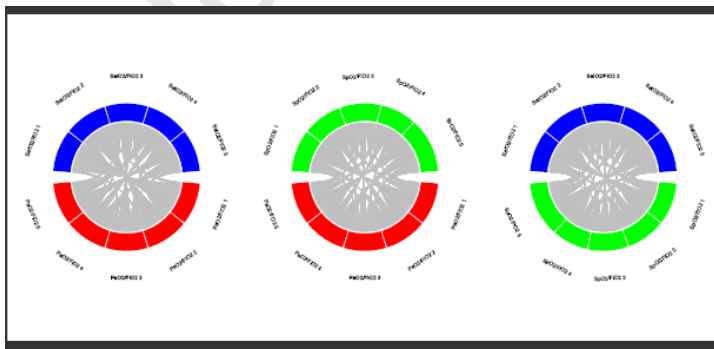
1. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. Solomon CG, editor. *N Engl J Med* 2020;383(25):2451-60.
2. The Lancet. Humanitarian crises in a global pandemic. *Lancet* 2020;396(10249):447.
3. Soto- Mota A, Marfil- Garza BA, Martínez Rodríguez E, Barreto Rodríguez JO, López Romo AE, Alberti Minutti P, et al. The low- harm score for predicting mortality in patients diagnosed with COVID- 19: A multicentric validation study. *J Am Coll Emerg Physicians Open* 2020;1(6):1436-43.
4. Núñez I, Priego-Ranero ÁA, García-González HB, Jiménez-Franco B, Bonilla-Hernández R, Domínguez-Cherit G, et al. Common hematological values predict unfavorable outcomes in hospitalized COVID-19 patients. *Clin Immunol* 2021;225:108682.
5. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ* 2020;m1328.
6. Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia Is Baffling to Physicians. *Am J Respir Crit Care Med* 2020;202(3):356-60.
7. Tobin MJ, Jubran A, Laghi F.  $P_{aO_2} / F_{IO_2}$  ratio: the mismeasure of oxygenation in COVID-19. *Eur Respir J* 2021;57(3):2100274.

8. Cao Z, Luo Z, Hou A, Nie Q, Xie B, An X, et al. Volume-Targeted Versus Pressure-Limited Noninvasive Ventilation in Subjects With Acute Hypercapnic Respiratory Failure: A Multicenter Randomized Controlled Trial. *Respiratory Care* 2016; 61 (11): 1440-1450.
9. Chan ED, Chan MM, Chan MM. Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations. *Respir Med* 2013;107(6):789-99.

**Figure 1. Correlation between oxygenation indexes.** SpO2: Oxygen saturation with pulse oximeter; PaO2: oxygen pressure in arterial blood; SatO2: oxygen saturation in arterial blood; FiO2: fraction of inspired oxygen.



**Figure 2. Variability of concordance between oxygenation indexes' quintiles.** SpO2: Oxygen saturation with pulse oximeter; PaO2: oxygen pressure in arterial blood; SatO2: oxygen saturation in arterial blood; FiO2: fraction of inspired oxygen. A) Shows relation between PaO2/FiO2 and SatO2/FiO2, B) shows relation between PaO2/FiO2 and SpO2/FiO2, and C) shows relation between SpO2/FiO2 and SatO2/FiO2. Numbers represent the respective quintile ("PaO2/FiO2 1" represents the first quintile of said variable).



Journal Pre-proof